REMARKS

Claims 11-22 are in the application. No claim is allowed.

Claims 11, 13 and 14 are rejected under 35 U.S.C. 102(b) as anticipated by Finkenaur et al., EP312208-A1 ("Finkenaur"). Reconsideration and withdrawal of this rejection are respectfully requested in view of the following. Claim 11 has been amended to recite that the composition, in addition to a growth factor and hyaluronic acid, contains excipients to maintain biological activity of the growth factor. This is supported in the specification at page 3, lines 1-7. The examiner cites example 4 on page 8 of Finkenaur as disclosing a composition comprising an effective amount of a growth factor (EGF) and hyaluronic acid (HA) having a viscosity of 44,000 cps. That formulation is alleged to have stimulated reendothelialization in the anterior chamber of the eye. The described composition contains only HA, the growth factor EGF and water. There are no excipients or other materials in the composition. Furthermore, in the general discussion of the invention from page 3, line 25 through page 6, line 18, there is no discussion in Finkenaur of excipients or other materials to be added to the composition other than the growth factor and the water soluble or water swellable polymer. In the other examples in Finkenaur there is no composition disclosed containing growth factor, hyaluronic acid and excipients. Therefore, Finkenaur does not anticipate the present claims and a withdrawal of the rejection is requested.

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finkenaur, of record. This rejection is respectfully traversed. Except for the anterior chamber of the eye, Finkenaur's compositions are intended for topical use for incisional wound healing. Therefore the compositions are not implanted. With respect to use in the eye, an extremely sensitive organ, as evidenced by the composition disclosed for use in example 4, no excipients are added with the hyaluronic acid and growth factor. Accordingly, it is submitted that one of ordinary skill in the art would not seek to modify Finkenaur's composition of example 4, since it is used in the eye. There

is no teaching in Finkenaur of use in bone or of implantation of a composition elsewhere in the body. Therefore, it is submitted that one of ordinary skill in the art would not be led to modify Finkenaur's composition of example 4 with excipients for implantation for the treatment of bone. Accordingly, it is submitted that the claims are unobvious over Finkenaur and reconsideration and withdrawal of the rejection are requested.

Claims 17-22 are rejected under 35 U.S.C. 103(a) as unpatentable over Dunstan et al., WO 95/24211 ("Dunstan") in view of Brismar, US 5,432,167 ("Brismar"). This rejection is respectfully traversed. The examiner states that Dunstan discloses a method of bone healing with bFGF, specifically referring to page 15 and the abstract of Dunstan. The method disclosed by Dunstan consists of applying 1 μg solutions of bFGF four times a day for three days over calavaria in mice. The issue of persistence of the bFGF at the site of desired growth is not addressed since the growth factor is reapplied eleven times over three days. The issue of biodegradability is not addressed since persistence at the site is not an issue. Hence, it is submitted that the teaching of Dunstan is to apply a solution of the growth factor directly at the site of the injured bone and to reapply it several times a day as long as it is needed. The experiment in Dunstan took place over three days, but presumably if one were treating a true fracture or defect, one would apply it over as many days, as required, to obtain the desired result of healing. Therefore, it is submitted that this teaching of Dunstan is to inject a solution of the growth factor directly at the site of desired bone growth several times a day.

In example 6 in Dunstan, FGF-1 was systemically administered to rat models of cortical and cancellous osteopenia. The bone mineral density in the femur, tibia and vertebrae were examined after 28 days of treatment. This suggests that if one were to treat other bones in the body other than the calavaria, repeated systemic injection would be the mode of administration.

There does not appear to be any motivation in Dunstan to modify these methods since the problems the present invention addresses do not appear in Dunstan.

Brismar does not provide a motivation to alter Dunstan, nor does it solve the defects in the teachings of Dunstan. Brismar discloses use of 0.1 to 2 % hyaluronic acid gels to treat varicose ulcers caused by diabetes. It is stated in column 1 that it is expected that the gel will promote osteoblast growth as well and could be used for the treatment of bone fractures. However, all of the tests and examples in Brismar are directed to treatment of ulcers caused by diabetes. The disclosed methods in Brismar are directed to topical administration to the ulcer. See col. 2, line 66 and col. 2, lines 22-30. It is stated that the gel is suitably effective by application once or twice a day and coverage by a bandage. It can be reasonably inferred that the bandage also contains the gel at the site. Moreover, by application of the gel directly to the bone fracture once or twice a day, this procedure can only be used for a compound fracture, since a treatment of simple fractures would not allow for topical administration. Furthermore, presumably a compound fracture would be reset before applying the gel and once the surface wound began heal, it would no longer be possible to topically apply the gel directly to the fracture. Accordingly, it is submitted to be a fair reading of Brismar that the gels disclosed therein are applicable only for topical administration through a wound or an open ulcer and that a bandage is needed to contain the gel at the wound site.. While it is suggested that the gel may be useful for bone fractures, there is no means disclosed how to apply it to a fracture, unless that fracture remains exposed in an open wound. The problem with persistence at the site it not even recognized by Brismar since the gel is reapplied once or twice daily and contained by a bandage. Issues of biodegradability of the hyaluronic acid at the site are not recognized by Brismar because the wound is presumably cleaned once or twice a day prior to the reapplication of the gel, thus removing what remained of the previously applied gel. Therefore,

Brismar does not solve the deficiencies of Dunstan in suggesting solutions of or recognizing the problem of how to maintain hyaluronic acid or a growth factor at a wound site after application without periodically reapplying it. Bismar does not solve the problem, much less recognize it, of how rapidly or slowly the body would absorb the hyaluronic acid by biodegradation, since Brismar reapplies fresh hyaluronic acid. Biodegradability never comes into question. Finally, there is no recognition by either Dunstan or Brismar of yet another problem of how to ensure that the growth factor, assuming that one would be led to apply growth factor to Brismar's gel, would persist at the site for a sufficient period of time to be of any use to the healing. As taught by Dunstan, the growth factor must be constantly reapplied several times a day. Therefore, one of ordinary skill in the art, in order to comply with Dunstan's requirement of reapplying the FGF, would also reapply the gel several times a day, a procedure that is also used by Brismar.

Therefore, there is simply no recognition by either Dunstan or Brismar of the desirability of applying a composition at the bone defect once and allowing the composition to persist at the site for a period of time sufficient to enhance the bone growth rate and magnitude. Moreover, according to the present invention, the hyaluronic acid dissipates from the site of application by biodegradation. Thus recognition of the biodegradation properties to match the required persistence at the bone defect are also features which Brismar and Dunstan fail to recognize and address.

For the foregoing reasons it is submitted that one of ordinary skill in the art would not be led to modify the method of Dunstan by the teachings of Brismar. Furthermore, even if one were to combine these teachings, one would be led to periodically remove and reapply the gel as taught both by Dunstan and Brismar, rather than to allow the composition to persist and dissipate by biodegradation. Furthermore, implantation to constantly contact the site of desired bone growth for the desired healing period is not a mode of application that is taught or contemplated by Brismar.

For the foregoing reasons it is submitted that the claims are unobvious over the combination of Dunstan and Brismar and withdrawal of the rejection is respectfully requested.

Claims 17-22 are rejected under the judicially created doctrine of double patenting over claims 1-5 of commonly owned US Patent No. 6,221,854 B1. Claims 11-22 are rejected under the judicially created doctrine of double patenting over claims 1-10 of commonly owned US Patent No. 5,942,499. Claims 11-15 are rejected under the judicially created doctrine of double patenting over claims 1-5 of commonly owned US Patent No. 6,703,377.

Terminal Disclaimers pursuant to 37 C.F.R. 1.321 are submitted herewith to obviate these obviousness-type double patenting rejections. Accordingly, it is respectfully requested that these rejections be withdrawn.

It is submitted that the claims are now in condition for allowance and passage to issuance is respectfully requested.

If prosecution of this application can be assisted by telephone, the Examiner is requested to call Applicants' undersigned attorney at (510) 663-1100.

Please apply any other charges or credits to deposit account number 50-388 (Order No. DEPYP003D1C1).

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Respectfully submitted,
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